A notable problem in the DNA investigating art is the quick reliable, efficient, and economical replication of the DNA chains. In the art, there are various ways, which are now "old fashioned" and no longer useful. See for example, our specification, page 1 , line 8- through - page 2, line 10. Also, in such art can be generally classified (but without specific similar teaching to replicate DNA chains) cited Balch, cited Haff and newly cited Ohkawa (although Ohkawa has nothing to do with DNA replication).

In other words, the market place is demanding instantaneous results for various problems including DNA replication. Before, the problem of DNA analysis was time consuming because DNA replication itself was time consuming, expensive, inefficient and unreliable.

Our invention accomplishes the foregoing goals by a novel and unobvious method and apparatus for carrying out such method, wherein polymerase chain reaction of biomolecules is accomplished in a plurality of capillaries which are disposed to have a gap between the open ends thereof and a substrate upon which the biomolecules are deposited so that there is no electric current flow therebetween, and then applying a voltage to the plurality fo capillaries and the substrate in its entirely so that a charge is placed on the biomolecules within the capillaries to cause the biomolecules to swell out from the bottom open ends of the capillaries and be deposited in very small amounts,in picoliter range, onto the surface of the substrate. The deposited biomolecules on the substrate form the biochips.

As shown, for example,in our FIG. 10(b), a negative charge

is placed on the biomolecule while in the capillary and then caused to"swell out" from the "bottom open ends" of the capillary, and by force of attraction caused to be deposited onto the substrate.

Note: We do not need any "wetting" electodes or "wetting" surface of the substrate, as do Balch, Haff and Ohkawa. Also, note: that the "electrostatic attraction forces (are) engaged between said biomolecules and said substrate before said biomolecules come into contact with said substrate". Advantageously, the charged biomolecules are caused to "swell out" from the bottom open ends and deposited onto the substrate in "very small volume". Moroever, please note: that advantageously, the voltage is not needed after the biomolecule is "swelled out" from the bottom open ends of the capillaries, to accomplish the depositing. Thus, clearly, the Blach discussion of the "continued flow of probe solution" by use of the electro-osmotic and/or electrophoretic forces" is not applicable or relevant. Moreover, substituting Ohkawa's teaching of voltage to move a droplet horizontally from one electrode to another for such teaching by Balch would not add anything to Balch which would make obvious applicant's use of the voltage to "swell out" the biomolecule from the bottom "open ends" of the "capillaries". Neither Balch nor Haff nor Ohkawa teaches anything about use of the voltage to "swell out" the biomolecule and cause its outward departure from the capillaries. This is done by "pressure" in Balch.. There is no teaching of same in Haff nor Ohkawa.

After the swelling out of biomolecule, there is deposition by attraction from the open ends to the substrate to accomplish in

our invention the "deposit""of a plurality of droplets of the "biomolecules" concurrently onto the "substrate" at "spaces" similar to the"predetermined spaces" between the "plurality of capillaries". Thus, the "biomolecules" are fixed onto the substrate at "fixed positions", and biochips are formed, efficienty, reliably, quickly, and inexpensively. Also, accuracy is guaranteeed.

To clarify certain wording, which may have been confusing to the Examine, what we mean by "applying a voltage across each of said plurality of capillaries and said substrate in its entirety during a depositing condition" means that we put the voltage to oppositely charge the capillaries and the biomoecules therein and the entire substrate (not parts thereof like in Ohkawa) to cause "electrostatic attractive forces to be engaged between said biomolecules and said substrate BEFORE said biomolecules come into contact with said substrate". That is to say, it is the electrostatic forces that cause the biomolecules to flow down through the capillaries and then to "swell out" from the "bottom open ends'. Then, the voltage is stopped, and the "droplets" fall down to the substrate by force of attraction and is fixed thereat at "spacings" which are similar to the "predetermined spacings" between the plurality of capillaries. In this manner,biochips are produced with the biomolecules being fixed on the substrate. Note, by this method, a controlled amount of very small volumes of biomolecules are deposited on fixed positions on the substrate. These are biochips wherein the DNA or similar biomolecules were subjected to PCR process in the plurality of capillaries in advance of the deposition. We

are not depositing "probe solutions" for later PCR processing in a reaction chamber, as is Balch. Haff merely discloses a number of ways to provide PCR processing, such as use of thermal baths and heat exchangers. Ohkawa merely moves droplets between two electrodes on the same plane using potential applied to the two electrodes. Thus, none of these cited references are related to or directed to the production of biochips, nor are they concerned with problems or objectives related thereto. Thus, even if combined, there would be no teaching in any of them singly or combined to provide a teaching which could be extended to make obvious the instant invention.

In Balch, the "probe solution" is force out of the capillaries by "pressure". Then, after the probe solution comes out, flow is continued by various means, such as adjustment of the height,etc, or "electro-osmotic and/or electro-phorentic force". There are no similar capillaries in Haff or Ohkawa from which solution is exited. Thus, only Balch need be considered on this point. However, as discussed above, the exiting of the probe solution is caused by pressure, not be voltage charging the droplet and causing same to "swell out" of the bottom open ends.

In contrast to Balch, Haff and Ohkawa, we use a novel approach to causing minute amounts of biomolecule to be deposited on a substrate, namely, the use of voltage to cause the biomolecule to flow down and "swell out" of the bottom open ends, and thus, be allowed to drop by force of attraction to the substrate. The voltage provides electrostatic attraction between the biomolecules and

substrate before any contact is made by the biomolecules and the substrate. In other words, we use the voltage to cause the exiting of the droplet from the plurality of capillaries. Then, the droplets are deposited onto the substrate without necessity of any electric to continue the flow downward.

That is, to put it simply, there are two parts to the movement of droplets. First, when the droplet breaks away from the open end. Then, second, when the droplet falls or continues movement downward to the substrate. We use voltage to accomplish the first part, and then we can stop the voltage and the droplet will fall by force of attraction to be deposited onto the substrate. In contrast, in Balch, the first part is accomplished by use of pressure. Then, instead of only a drop of very small amount, Balch has a continuous flow of "probe solution". That second part, or continued flow is accomplished by adjustment of height, electro-osmotic force, and/or electro-phorentic forces. But, note, Balch does not teach or suggest any specific way, means,etc, of such use of electro-osmotic and/or electro-phorentic forces. Haff and Ohkawa has no teaching regarding such first part or second part of the depositing.

Thus, clearly, even if the three references were combined, there is still lacking that use of voltage for the first part of the depositing process. Moreover, there is no teaching in any of the three that appreciates how the depositing process occurs and the way to solve the problem, that is for very small amounts . Note, Balch is for larger amounts of "probe solution" which is placed upon the "reaction vessell" then reacted. It is not a process for

producing biochips comprising a substrate (not reaction vessel as in Balch) on which are deposited small amounts of biomolecultes. Ohkawa has no inkling of any problem related to our invention since he merely teaches how to move a doplet from one electrode horizontally to another ellectrode, both of which electrodes are wettable. Haff only teaches use of thermal baths and heat exchangers to carry out polymerase chain reaction.

Thus, essentially, at a key point of our invention, only Balch has any teaching which might be relevant. However, at the initial depositing point, Balch uses pressure... We use voltage in a manner never before done. There is no teaching anywhere including Ohkawa where voltage is use din the manner recited in our new claims, nor any art shown which provides the results provided by our recited invention.

As above mentioned, we do not need to continue application of voltage to continue the downward dropping of the droplet once voltage causes same to "swell out" of the bottom open ends of the plurality of capillaries. In contrast, Balch's method must use some method to continue flow of the probe solution. His probe solution is of larger quantities... our droplet is in very small volumes, in the order of "picoliters". This is all that is necessary when fixing amounts of biomolecules on a chip. On the other hand, Balch's probe solution requires greater quantities, and further reaction. The reaction vessel is NOT a substrate of a biochip as in our invention. In contrast to the art, including Balch, we are able to deposit very small volume of biomolecules on the substrate.

On the other hand, Balch's objective is to create a "multiplexed molecular array", which is later reacted as desired. It is only necessary to force large volumes of "probe solutions" for tubes onto the "reaction vessel." for later reaction. Thus, pressure is most appropriate for his apparatus. He does not need to deposit very small amounts of volume of biomolecules onto chips.

Haff has relevance only in that he discloses methods of carrying out PCR (polymerase chain reaction) using thermal baths, and/or heat exchangers. Thus, even if Haff is combined with Balch, there is nothing new added to the prior art. However, since Balch disclosues a method for placing probe solution onto a reaction vessel and then using, for example, a reaction processing on the depositted probe solution, adding Haff really adds nothing to Balch, he implicitly carries out a PCR reaction after depositing the probe solution onto biosites on the reaction vessel.

Ohkawa has relevance in using two horizontal electrodes to move a droplet on one electrode to the other by applying voltaga to the two electrode. BUT, there is no teaching in Ohkawa, of using voltage to cause the "swelling out" of "biomolecules" in a "plurality of capillaries" through "bottom open ends thereof" with the "electrostatic attractive forces engaged between said biomolecules and said substrate before said biomolecules come into contact with said substrate". Ohkawa's droplet travels horizontally from electrode to electrode.. not from and through an open end then after leaving the open end to be deposited onto a substrate. There is no way a person skilled in the art could make that leap in logic from the Ohkawa disclosure.

Although the Examiner's detailed allegations (which attorney has studied in detail and greatly appreciates) seem to be fitted to the wording of the claims, in point of fact, it would appear that the rejections are based on rejection of a broader concept of DNA replication using a plurality of capillaries to deposit biomolecules on a substrate. But, we have set forth in great detail the inner workings of the voltage application and its effect on the depositing process for creation of biochips. The Balch disclosure is slightly different. It is not used directly for creating biochips, as above discussed. But, also more importantly, at the esssential point of the invention, that is the point of exiting of the biomolecule from the"bottom open ends" of the "plurality of capillaries", there is no teaching at all in the prior art which is the use of voltage to "swell out" the biomolecule through the open ends, so that a "very small volume" of the biomolecule can be depsited and fixed in positions on the substrate to thereby create biochips of DNA,etc.

The Examiner has newly cited Ohkawa as showing applicatinn of voltage across a capillary and a substrate, and concludes that since at col. 15, lines 43-52, Balch discusses use of "electro-osmotic and/or electro-phorentic forces", combining the two would make obvious applicant's use of the voltage. The Examiner is believed to be in error of facts and hence has drawn the wrong conclusion.

As above discussed, at the point where the "probe solution" is forced from the capillary end, the force causing same is PRESSURE. It is not electro-osmotic and/or electro-phorentic forces. This

latter force is used after the probe solution is exited from the opening, and is used to "continue the flow'. Thus, substituting Ohkawa at this point still leaves missing the essential feature missing... that is even if combined, Ohkawa and Balch and Haff still has missing the use of voltage to cause "swelling out" of the "biomolecule" from the "open end" of the "capllary". They would still be using "pressure" to cause the "probe solution" to exit the open end.

Furthermore, Ohkawa does not show or suggest any use of voltage between an open end of a capillary and a substrate. At best, Ohkawa shows use of two horizontal wettable electrodes on the same plane and a droplet placed on one electrode which is moved to the other electrode when voltage is applied to both electrodes. Even if extended, there is nothing in Ohkawa to suggest using the voltage for the purpose recited in our claims, anmely to cause "swelling out" of the "biomolecules" from the "open ends of the plurality of capillaries" and by force of attraction caused to be deposited in very small amounts onto the substrate at fixed positions.

In another embodiment of Ohkawa, he uses one or more electrodes on the surface of a substrate, and deposits a droplet in a manner wherein the droplet is attracted to the electrode when voltage is applied. In this manner Ohkawa accurately places the droplet on the electrode of the substrate surface. Clearly, even this embodiment has nothing to do with the instant invention, wherein the voltage acts upon the droplet at the open ends of the capillaries to

cause the droplets to "swell out" and exit the open ends by the charge placed thereon.

In view of the foregoing, clearly, there is no section 103 obviousness of the method claims of claims 48-50 by the combined references Balch, Haff and Ohkawa.

For similar reasons, it is believed that there is no section 103 obviousness by the cited references in combination. The apparatus claims 51-53 recite means for carrying out the method of clams 48-50 and in addition adds a "means for adjusting the gaps".

DOUBLE PATENTING OBJECTION

In view of the closeness of the instant application and SN 09/792,967, applicant is abandoning 09/792,967. Thus, there is no longer any outstanding issue and no disclaimer is required.

In view of the foregoing, applicant respectfully solicits reconsideration and allowance.

Respectfully
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SN - 09/792,967

FILED - 2/26/01

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Sirs:

Applicant herein hereby voluntarily abandons the above application.

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